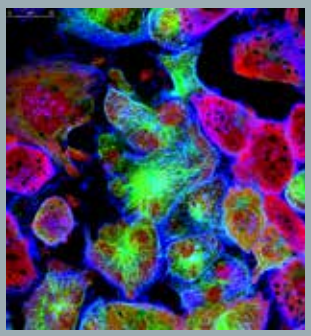
CDMRP

Department of Defense

Breast Cancer Research Semipostal Program



U.S. Army Medical Research and Materiel Command

PROTECT · PROJECT · SUSTAIN

Congressionally Directed Medical Research Programs

HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has managed over $10.8 billion in research funds from its inception through fiscal year 2016 (FY16). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Breast Cancer Research Program (BCRP), is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

Breast Cancer Research Semipostal Program

About the Program

As a result of the efforts of breast cancer advocates, the Stamp Out Breast Cancer Act (Public Law No. 105-41) led to the U.S. Postal Service's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS) in 1998. It was the first semipostal stamp in U.S. history. Net revenues from sales of the BCRS, which costs 60 cents, are provided to two designated funding agencies, the DoD BCRP and the National Institutes of Health, to support breast cancer research. The Breast Cancer Research Stamp Reauthorization Act of 2015 (Public Law No. 114-99) reauthorized the stamp through December 31, 2019.

Research and Management Costs

Breast cancer stamp funding received by the BCRP between FY99 and FY15 has been used to fully or partially fund 62 awards under three award mechanisms: the Idea Award, Synergistic Idea Award, and Breakthrough Award Funding Level 1 (Figures 1A and 1B). These award mechanisms support innovative, high-risk, high-reward research that could lead to major advancements in breast cancer. Applications funded through the BCRS Program were reviewed and recommended for funding according to the two-tier review system implemented by the DoD BCRP. An evaluation of the awards funded through the BCRS Program shows that the projects encompass a diversity of research areas (Figure 2).

Total Proceeds from BCRS	**$24,140,455**
Research	$22,973,598
Management Costs	$1,166,857

Figure 1A. BCRS Research and Management Costs, FY99–FY15

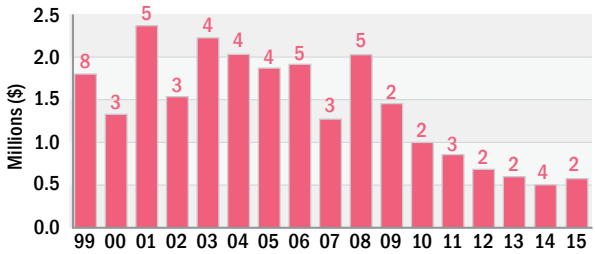


Figure 1B. BCRS Funding and Number of Awards Supported, by Fiscal Year

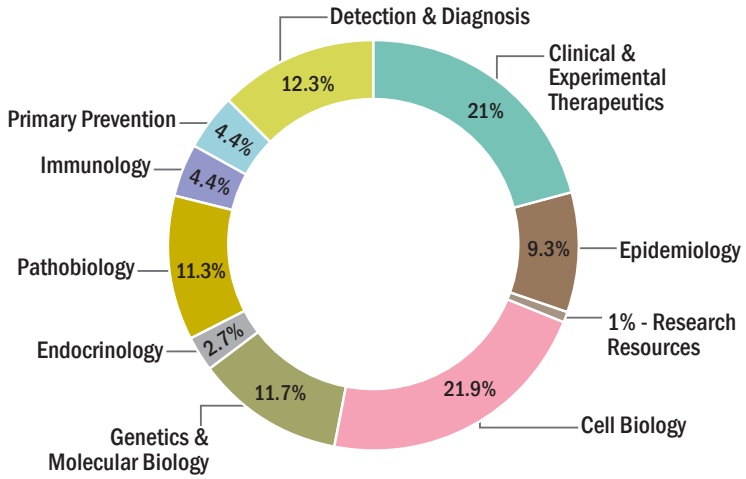
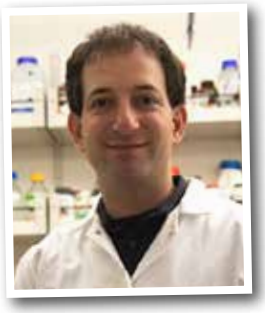


Figure 2. BCRS Award Portfolio Composition, by Percent of Funding Invested

Recent Research Advancements



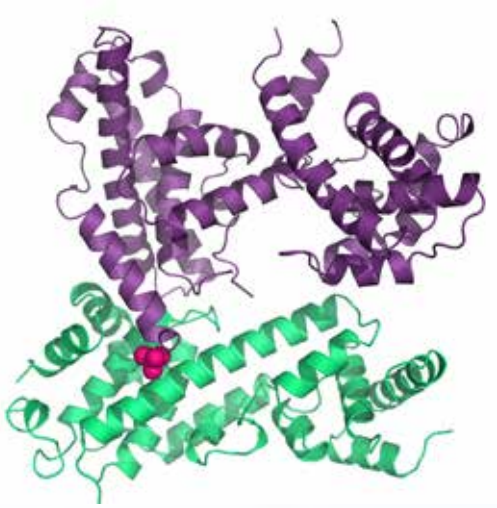
A Strategy for Direct Chemical Activation of the Retinoblastoma Protein

Seth M. Rubin, Ph.D., University of California, Santa Cruz

The retinoblastoma (Rb) protein pathway, a tumor suppressive network, coordinates cellular growth signals with cell cycle progression and almost invariably is altered in breast cancer cells. Rb regulates cell cycle progression by interacting with transcription factor E2F and, ultimately, keeping cell proliferation in check. A conformational change occurs upon Rb phosphorylation by an enzyme called cyclin-dependent kinase 4/6 (cdk4/6), thus inhibiting E2F binding to Rb. E2F dissociation from Rb enables E2F-dependent cell cycle progression and proliferation. While many cancers have genetic mutations within the Rb gene locus, breast tumors instead have a tendency for upregulated cdk4/6 protein levels, leading to ubiquitous phosphorylation of Rb, resulting in uncontrolled cell cycle progression and tumor cell proliferation.

Dr. Seth Rubin and his team undertook a novel transformative approach to potentially restore Rb pathway function. With support from an FY13 Breakthrough Award funded by the BCRS Program, Dr. Rubin sought to show for the first time that the Rb pathway could be reactivated through direct targeting of Rb to enhance its binding to E2F in the presence of upregulated cdk4/6 activity.

Dr. Rubin's work, published this year in *ACS Chemical Biology*, used an elegant quantitative fluorescent polarization (FP) assay to demonstrate that a peptide derived from the Human Papilloma Virus (HPV) E7 was capable of increasing the binding affinity of phosphorylated Rb to E2F. Dr. Rubin showed, using the FP assay, that in the presence of the HPV E7 peptide, phosphorylated Rb bound to E2F with similar affinity as unphosphorylated Rb. Moreover, using the higher-affinity, full-length HPV E7 protein, phosphorylated Rb bound E2F with a twofold higher affinity than unphosphorylated Rb alone, implicating the HPV E7 peptide as an Rb activator molecule. To confirm the specificity of the interaction, Dr. Rubin mutated two key amino acid residues within the pocket domain and found that the HPV E7 peptide was not able to promote E2F binding to Rb in any conditions.



The information obtained through this innovative research has the potential to open a new avenue of research on peptides or small molecules that specifically reactivate the Rb tumor suppressive pathway and bypass upstream cdk-dependent signaling to inhibit breast tumor cell proliferation.

Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk

Peggy Reynolds, M.P.H., Ph.D., Cancer Prevention Institute of California

Breast cancer incidence rates vary dramatically by geographic region, suggesting that exposure to environmental factors, such as urban air pollution, could play a role in the etiology of breast cancer. Numerous chemicals found in air pollution have been shown to increase mammary gland tumor development in mice or to act as estrogen disruptors, but few studies have explored this risk in human populations. With support from an FY09 Idea Award funded by the BCRP and the BCRS Program, Dr. Peggy Reynolds examined the association of breast cancer and residential exposure to a variety of hazardous air pollutants (HAPs), including potential carcinogens and estrogen disruptors.

In this study, Dr. Reynolds assessed the relationship between breast cancer incidence rates in a prospective cohort of over 112,000 women living in California and estimated outdoor concentrations of HAPs on a census tract level, as modeled by the United States Environmental Protection Agency. This study was unique in that it was the first to examine quantitatively the relationship between ambient exposure to potential mammary gland carcinogens or estrogen disruptors and breast cancer incidence on the individual level. Among the potentially carcinogenic HAPs, a statistically significant increase in breast cancer risk was observed for women residing in areas with high estimated concentrations of propylene oxide and vinyl chloride. Additional HAPs were associated with increased incidence of breast cancer, based on the hormone responsiveness of the patient's tumor. Estrogen receptor-positive or progesterone receptor-positive (ER+/PR+) tumors were associated with higher ambient levels of acrylamide, benzidine, carbon tetrachloride, ethylidene dichloride, and vinyl chloride, while ER-/PR- tumors were associated with higher ambient levels of benzene. Among the estrogen-disrupting HAPs, higher levels of cadmium and inorganic arsenic were associated with ER-/PR- tumors in residentially stable, non-smoking women.

Findings from this study suggest that environmental exposure to a variety of air pollutants could contribute to an increased risk of breast cancer in some women. This work represents an important foundation for more environmental research to evaluate further the risk associated with HAPs and their potential interplay with tumor hormone signaling.

Noninvasive Label-Free Detection of Micro-metastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging

Dr. Geoffrey Luke, Thayer School of Engineering, Dartmouth College

Over 90% of cancer-related deaths can be attributed to metastasis, and determining whether cancer has spread is critical to selecting the right treatment strategy. The standard method is to biopsy the first node to which the primary tumor drains, called the sentinel lymph node (SLN). However, SLN biopsies are invasive procedures that expose the patient to radioactive compounds, have a high level of morbidity, and may require 2 or more weeks to obtain results. In FY13, Dr. Geoffrey Luke received a Breakthrough Award funded by the BCRP and BCRS Program to develop a combined ultrasound/photoacoustic (US/sPA) imaging device to detect micro-metastases in the lymph nodes of breast cancer patients.

In sPA imaging, a pulse of light is sent into tissue, causing it to expand slightly and creating an US wave. When this wave is detected with a standard US transducer, its properties reveal chemical information about the tissue, especially whether the blood contains oxygen. Once a primary tumor is detected, sPA imaging, when coupled with traditional US imaging, has the potential to provide physicians with comprehensive anatomic and functional information about regional lymph nodes.

The goal of Dr. Luke's research is to transform the metastasis detection process for breast cancer patients, reducing and ultimately eliminating the need for painful SLN biopsies. This breakthrough system requires no external contrast agent, delivers no ionizing radiation, and can generate high-resolution images at a depth of several centimeters in real time.

Dr. Luke has used the combined US/sPA imaging system to monitor the functional changes that occur with the onset of lymph node metastases in a mouse model of breast cancer. In a previous study of oral cancer, Dr. Luke found a significant decrease in SLN blood oxygen saturation, with an increase in histologically confirmed metastasis, and current experiments in breast cancer mice are showing the same trends. Dr. Luke is also improving the sensitivity and specificity of his sPA/US system in preparation for upcoming breast cancer human studies. In patients with a diagnosis of primary tumor, US examination of lymph nodes combined with sPA imaging may result in a sensitive, noninvasive clinical tool capable of detecting small metastases, enabling clinicians and patients to make informed decisions about treatment regimens.

Recent Publications Resulting from BCRS-Funded Research

Kim JA, Tan Y, Wang X, et al. 2016. Comprehensive functional analysis of the tousled-like kinase 2 frequently amplified in aggressive luminal breast cancers. *Nat Commun.* 7:12991.

Pye CR, Bray WM, Brown ER, et al. 2016. A strategy for direct chemical activation of the retinoblastoma protein. *ACS Chem Biol.* 11:1192-1197.

Liu R, Nelson DO, Hurley S, et al. 2015. Residential exposure to estrogen disrupting hazardous air pollutants and breast cancer risk: the California Teachers Study. *Epidemiology.* 26(3):365-373.

Garcia E, Hurley S, Nelson DO, et al. 2015. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health.* 14:14.

Shu D, Li H, Xiong G, et al. 2015. Systemic delivery of anti-miRNA for suppression of triple negative breast cancer utilizing RNA nanotechnology. *ACS Nano* 9(10):9731-9740.

Luke GP, Emelianov SY. 2015. Label-free detection of lymph node metastases with US-guided functional photoacoustic imaging. *Radiology.* 277(2):435-442.

Martinson HA, Jindal S, Durand-Rougely C, et al. 2015. Wound healing-like immune program facilitates postpartum mammary gland involution and tumor progression. *Int J Cancer.* 136(8):1803-1813.

Wei SC, Fattet L, Tsai JH, et al. 2015. Matrix stiffness drives epithelial-mesenchymal transition and tumour metastasis through a TWIST1-G3BP2 mechanotransduction pathway. *Nat Cell Biol.* 17(5):678-688.

Boelens MC, Wu TJ, Nabet BY, et al. 2014. Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell.* 159(3):499-513.

Boras-Granic K, Dann P, Vanhouten J, et al. 2014. Deletion of the nuclear localization sequences and C-terminus of PTHrP impairs embryonic mammary development but also inhibits PTHrP production. *PLoS One.* 9(5):e90418.

Veeraraghavan J, Tan Y, Cao XX, et al. 2014. Recurrent ESR1-CCDC170 rearrangements in an aggressive subset of estrogen receptor-positive breast cancers. *Nat Commun.* 5:4577.

BCRS Program Funded Awards

FY	PI	Amount	Institution	Proposal Title
FY99	Daly	$283,649	Garvan Institute	Identification of Novel Prognostic Indicators for Breast Cancer Through Analysis of the EMS1/Cortactin Signaling Pathway
	Deuel	$5,000[1]	Scripps Institute	Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor-Promoting Pathways in Human Breast Cancer
	Heyer	$111,444	University of California, Davis	In Vitro Recombination Activities of the Breast Cancer Predisposition Protein BRCA2
	Musgrove	$222,652	Garvan Institute	Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland in Vivo
	Shah	$279,000	University of Arkansas	Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion
	Wang	$317,510	Texas A&M University	Scanning Microwave-Induced Acoustic Tomography
	White	$334,094	University of Texas Southwest Medical Center	Isolation of Factors That Disrupt Critical Protein/Protein Interactions Within the Telomerase Holoenzyme for Use in Breast Cancer Therapeutics
	Wreschner	$225,000	Tel Aviv University	Analysis of the Secreted Novel Breast Cancer-Associated MUC1/Zs Cytokine
FY00	Adamson	$578,183	Burnham Institute	Cripto: A Target for Breast Cancer Treatment
	Akporiaye	$454,500	University of Arizona	Tumor-Mediated Suppression of Dendritic Cell Vaccines
	Penn	$296,142	University of Toronto	Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein
FY01	Cai	$560,144	Vanderbilt University	Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk
	Carraway	$427,225	University of California, Davis	Identification of a Functional Human Homolog of Drosophila Kek1, an Inhibitor of Breast Tumor Cell Growth
	Chaudhary	$312,000	University of Texas Southwest Medical Center	The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer
	Geahlen	$425,425	Purdue University	Characterization of Syk in Breast Carcinoma Cells
	Rosner	$454,181	St. Luke's-Roosevelt Hospital Center	Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin
FY02	Dou	$491,999	University of South Florida	Synthetic Beta-Lactam Antibiotics as a Selective Breast Cancer Cell Apoptosis Inducer: Significance in Breast Cancer Prevention and Treatment
	Godwin	$504,000	Fox Chase Cancer Center	The Nuclear Death Domain Protein p84N5, a Candidate Breast Cancer Susceptibility Gene
	Perkins	$490,500	Yale University	Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer
FY03	Chung	$490,447	Yale University	Quantitative in Situ Assessment of the Somatostatin Receptor in Breast Cancer to Assess Response to Targeted Therapy with 111-in-Pentetreotide
	Kaaks	$367,639	International Agency for Cancer Research	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk: A Study Within the European Prospective Investigation into Cancer and Nutrition (EPIC)
	Yaswen	$508,790	Lawrence Berkeley National Laboratory	Functional Analysis of BORIS, a Novel DNA-Binding Protein
	Ziv	$767,171	University of California, San Francisco	Admixture and Breast Cancer Risk Among Latinas
FY04	Bissell	$386,569	Lawrence Berkeley National Laboratory	Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors
	Clarke	$588,738	Northern California Cancer Center	The Hygiene Hypothesis and Breast Cancer: A Novel Application of an Etiologic Theory for Allergies, Asthma, and Other Immune Disorders
	Giorgio	$453,000	Vanderbilt University	Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer
	Lemmon	$475,500	University of Pennsylvania	Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment
FY05	Zinn[2]	$436,500	University of Alabama at Birmingham	Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Model
	Huang	$483,600	Cornell University, Weill Medical College	Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis
	Liu	$448,500	Ohio State University	Hunting for Novel X-Linked Breast Cancer Suppressor Genes in Mouse and Human
	Rao	$468,000	Stanford University	Ribozyme-Mediated Imaging of Oncogene Expression in Breast Tumor Cells

FY	PI	Amount	Institution	Proposal Title
FY06	Devi	$155,085[3]	Duke University Medical Center	Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy
	Lee	$489,000	University of Southern California	A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer
	Li	$438,455	Baylor College of Medicine	The ER/PR Status of the Originating Cell of ER-Negative Breast Cancer
	Mousa	$377,620	Albany College of Pharmacy	Enhancing the Efficacy of Chemotherapeutic Breast Cancer Treatment with Non-Anticoagulant Heparins
	Rastinejad	$454,500	University of Virginia	Structural Characterization of the Interdomain Features of the Estrogen Receptor
FY07	Kuperwasser	$817,500	Tufts University	Mechanisms of Breast Cancer Associated with Obesity
	Kelly	$244,450[4]	University of Virginia	Genetically Encoded Targeted, Amplifiable, Imaging Agents for Early Detection of Breast Cancer
	Gerbi	$155,550[5]	Brown University	Hormonal Involvement in Breast Cancer Gene Amplification
FY08	Park	$111,663	North Dakota State University	In Utero Exposure to Dietary Methyl Nutrients and Breast Cancer Risk in Offspring
	Radosz	$528,939	University of Wyoming	Breast Cancer-Targeting Nuclear Drug Delivery Overcoming Drug Resistance for Breast Cancer Therapy
	Hill	$577,500	Oregon Health and Science University	Vaccine Vector for Sustained High-Level Antitumor CTL Response
	You	$503,666	University of Oklahoma Health Science Center	Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents
	Seagroves	$166,667[6]	University of Tennessee Health Science Center	The Role of HIF-1 Alpha in Breast Cancer: A Positive Factor in Cancer Stem Cell Expansion via Notch?
FY09	Reynolds	$730,000[7]	Cancer Prevention Institute of California	Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk
	Wysolmerski	$620,626	Yale University	Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer
FY10	Schedin	$368,125[8]	University of Colorado, Denver	The Immune Modulatory Program of Post-Partum Involution Promotes Pregnancy-Associated Breast Cancer
	Leung	$556,875[9]	Johns Hopkins University	The Role of Poly(ADP-Ribose) in microRNA Activity in Breast Cancers
FY11	Minn	$399,942	University of Pennsylvania	Regulation of Metastasis and DNA Damage Resistance Pathways by Transposable Elements
	Wang	$409,693	Baylor College of Medicine	Copy Number Signature of Recurrent Gene Fusions Reveals Potential Drug Targets in Invasive Breast Cancer
	Gonzalo Hervas	$58,975[10]	St. Louis University	Stabilization of 53BP1 in Triple-Negative and BRCA-Deficient Breast Tumors: A Novel Therapeutic Strategy
FY12	Yang	$465,000	University of California, San Diego	Regulation of Breast Cancer Stem Cell by Tissue Rigidity
	Giancotti	$174,837[11]	Memorial Sloan-Kettering Cancer Center	Autophagy and TGF-Beta Antagonist Signaling in Breast Cancer Dormancy at Premetastatic Sites
FY13	Rubin	$457,075	University of California, Santa Cruz	Inhibition of Retinoblastoma Protein Inhibition
	Luke	$96,992[12]	University of Texas at Austin	Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging
FY14	Shu	$364,343	University of Kentucky	Ultrastable Nontoxic RNA Nanoparticles for Targeting Triple-Negative Breast Cancer Stem Cells
	Ellisen	$93,050[13]	Massachusetts General Hospital	Defining High-Risk Precursor Signaling to Advance Breast Cancer Risk Assessment and Prevention
	Brown	$7,457[14]	University of Rochester	Prediction of Metastasis Using Second Harmonic Generation
	DeNardo	$7,061[15]	Washington University	Reprogramming the Metastatic Microenvironment to Combat Disease Recurrence
FY15	Bonfil	$254,765[16]	Wayne State University	Discoidin Domain Receptors: Novel Targets in Breast Cancer Bone Metastasis
	Maki	$254,765[17]	Rush University Medical Center	Targeting Prolyl Peptidases in Triple-Negative Breast Cancer

[1] Total award amount was $404,176; remaining funds were from the FY99 BCRP.
[2] The original Principal Investigator, Dr. Tandra Chaudhuri, is deceased.
[3] Total award amount was $461,933; remaining funds were from the FY06 BCRP.
[4] Total award amount was $687,397; remaining funds were from the FY06 BCRP.
[5] Total award amount was $787,325; remaining funds were from the FY06 and FY07 BCRP.
[6] Total award amount was $554,987; remaining funds were from the FY08 BCRP.
[7] Total award amount was $860,883; remaining funds were from the FY09 BCRP.
[8] Total award amount was $556,028; remaining funds were from the FY10 BCRP.
[9] Total award amount was $585,652; remaining funds were from the FY10 BCRP.
[10] Total award amount was $744,661; remaining funds were from the FY11 BCRP.
[11] Total award amount was $331,449; remaining funds were from the FY12 BCRP.
[12] Total award amount was $497,288; remaining funds were from the FY13 BCRP.
[13] Total award amount was $605,208; remaining funds were from the FY14 BCRP.
[14] Total award amount was $216,085; remaining funds were from the FY14 BCRP.
[15] Total award amount was $527,797; remaining funds were from the FY14 BCRP.
[16] Total award amount was $522,715; remaining funds were from the FY15 BCRP.
[17] Total award amount was $581,250; remaining funds were from the FY15 BCRP.

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